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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/381,497	02/17/00	FITZGERALD D	015280-31710

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EXAMINER	
HELMS,I	
ART UNIT	**PAPER NUMBER**
1642	14

DATE MAILED: 07/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/381,497	FitzGerald et al
Examiner	**Art Unit**
Larry R. Helms Ph.D.	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *10 May 2001*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-17, 22-32, and 40-49* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-17, 22-32, and 40-49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a☐ approved b)☐disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b) ☐ Some* c) ☐None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Claims 1-17, 22-32, and 40-49 are pending.

Claims 1, 5-8, 11-12, 15, 22, 27-30 have been amended.

Claims 40-49 have been added.

Claims 1-17, 22-32, and 40-49 are under examination.

2. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.

3. The following Office Action contains some NEW GROUNDS of rejection

Rejections Withdrawn

4. The rejection of claims 1-10, 12, 15-16, 18-39 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

5. The rejection of claims 6, 8-10, 15-21, 28, and 33-39 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the new sequence listing.

6. The rejection of claims 1-5, 7-14, 17-19, 22-24, 26-27, 29-32, and 39 under 35 U.S.C. 112, first paragraph is withdrawn in view of the amendments to the claims and arguments.

7. The rejection of claims 5, 12, and 27 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of the amendments to the claims.

8. The rejection of claims 6, 8-10, 15-21, 28, and 33-39 under 35 U.S.C. 102(b) as being anticipated by Fitzgerald et al (WO 98/41641, published 9/24/98) is withdrawn.

9. The rejection of claims 6, 8, 10, 18, 19, 28, 33, 35-37 under 35 U.S.C. 102(b) as being anticipated by Kreitman et al (Proc. Of the American Association for Cancer Res. 38:28, 1997) is withdrawn.

Response to Arguments

10. The rejection of claims 1-17, 22-32, and newly submitted claims 40-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96) is maintained and made again.

The response filed 5/7/01 has been carefully considered but is deemed not to be persuasive. The response states "the constructs of Ghetie were created by chemical conjugation

methods" and "at the time of the invention, the recombinant immunotoxin could not have been made in the absence of knowledge of the nucleic acid and amino acid sequences". In response to these arguments, the references of both Kuan et al and Reiter et al teach recombinant immunotoxins and also it would have been obvious to one of skill in the art at the time the claimed invention was made to obtain the nucleic acid and the amino acid sequence for the VH and VL using primers and techniques known in the art. Thus, it would be obvious that the antibody of Ghetie et al would have the sequence of the VH of SEQ ID NO:2 and a VL of SEQ ID NO:4. In addition, one skilled in the art would know that one can produce conservative substitutions in the amino acid sequence to produce antibodies that can bind CD22.

The following are some NEW GROUNDS of rejections

11. Claims 42-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42-47 are indefinite for reciting "conservatively modified variant" because the exact meaning of the phrase is not clear. It is not clear how the VH or VL is "modified" to result in the "variant" recited in the claims. In addition, the claims are indefinite for reciting "variant" as the exact meaning of the word is not known. The term "variant" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable

meaning for said phrase. Since it is unclear how the VH and the VL are to be "modified" to yield the class of "variants" referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "variant" of the antibody is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "variant" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

12. Claims 5-6, 8-10, 12, 15-16, 27-28, and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunoconjugate comprising a toxin of PE or PE38 or a detectable label peptide linked to a recombinant anti-CD22 antibody of RFB4 with a VL of SEQ ID NO:4 which contains a cysteine at amino acid position 100 and a VH of SEQ ID NO:2 with a cysteine at position 44, wherein the VH chain is covalently attached to the amino terminus of PE or PE38 and the VL and VH are linked through a liner peptide of SEQ ID NO:5 or through a cysteine-cysteine disulfide bond, does not reasonably provide enablement for any immunoconjugate that binds to the same epitope as RFB4 or an immunoconjugate comprising a VH or VL with 90% identical to SEQ ID NO:2 or 4. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any antibody that binds the same epitope of RFB4 and any VH or VL that are at least 90% identical to SEQ ID NO:2 and 4.

The specification teaches the RFB4 antibody which comprises a cysteine at position 44 in the VH and a cysteine at position 100 in the VL covalently coupled to PE (PE38) wherein the VH is SEQ ID NO:2 and the VL is SEQ ID NO:4.

The claims are not commensurate in scope with the enablement provided in the specification. As taught in Greenspan et al (Nature Biotechnology 7:936-937 (1999)) defining epitopes is not as easy as it seems (page 937). Epitopes have been defined in terms of the spacial organization of residues that make contact with a ligand and the structural characterization of the molecular interface for the binding of the molecules to define the epitope boundaries (page 937 middle of page). The epitope defined in this manner will likely include residues that contact the ligand but are energetically neutral or even destabilizing to binding. "In addition, a priori it will

not include any residue that makes no contact with a ligand but whose substitution may profoundly effect ligand recognition through influence on the stability of the free form of the macromolecule, or participation in long-range allosteric effects". "Even when the residues making contacts with ligands are known with certainty, say from the crystal structure of the complex, the question remains with regard to the energetic involvement of each residue (page 936 right column, first paragraph). Therefore, "amino acids should be recognized to have multiple ways of contributing to a noncovalent interaction" (page 937, middle of page). The specification does not teach epitope mapping of the RFB4 antibody and as such one would not know if an antibody binds to the same epitope as RFB4. As evidenced by Greenspan et al a number of factors not primarily related to the contours of the contacts of the molecules contribute to the free energy change, sometimes profoundly.

Claims 6, 15, 28 are broadly drawn to any antibody with a VH and a VL that is at least 90% denticle to SEQ ID NO:2 or 4. Sequence identity between two sequences has no common meaning within the art. See George et al; "Current Methods in Sequence Comparison and Analysis", in Macromolecular Sequencing and Synthesis, Selected Methods and Applications, pages 127-149 1988, Alan R. Liss, Inc and Barton et al "Protein Sequence Alignment and Database Scanning" in Protein Structure Prediction, A Practical Approach, 1996 IRL Press at Oxford University Press, Oxford, UK, pages 31-63). Barton et al teach that the "results of the analysis are entirely dependent on the choice of scoring results" (page 130, col 1-2, bridging paragraph). George et al teach that percent sequence identity is not an objective property of

molecules but is a value arrived at by using algorithms (page 130, columns 1-2, bridging paragraph). The scoring of gaps when comparing one nucleic acid sequence to another introduces uncertainty as to the percent of similarity between two sequences and applies equally to comparison of amino acid sequences. The specification teaches a variety of algorithms for sequence (see page 14) however the specification apparently lacks any particular guidance or specific method for determining 90% sequence identity. Therefore, it remains unclear what sort of alignment is allowed (i.e., gaps, mismatches) and which amino acid residues are considered to be similar. Thus, one cannot therefore determine how to make and use molecules which have "90% sequence identity".

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Conclusions

13. No Claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

SHEELA HUFF
PRIMARY EXAMINER